TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System

STERILE: Sterilized with dry heat, ethylene oxide and radiation. For one use only. Do not resterilize.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

DESCRIPTION

The TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is an artificial embolization device, comprised of TRUFILL® n-Butyl Cyanoacrylate (n-BCA), TRUFILL® Ethiodized Oil and TRUFILL® Tantalum Powder. These components must be used as a system. They are not intended to be used as individual components. The TRUFILL® n-BCA Liquid Embolic System is used under fluoroscopic guidance to obstruct or reduce the blood flow to cerebral arteriovenous malformations (AVMs) via superselective catheter delivery. Upon contact with body fluids or tissue, the mixture polymerizes into a solid material.

The TRUFILL® n-BCA monomer is a clear, free-flowing liquid that polymerizes via an anionic mechanism. TRUFILL® Ethiodized Oil is a straw to amber colored, oily fluid containing iodinated poppyseed oil used as a radiopaque polymerizing retardant. The amount of TRUFILL® Ethiodized Oil used will vary the rate of polymerization of TRUFILL® n-BCA. TRUFILL® Tantalum Powder is a finely ground, irregularly shaped, dark gray metal that may be used with TRUFILL® Ethiodized Oil to radiopacify TRUFILL® n-BCA.

INTENDED USE/INDICATIONS

The TRUFILL® n-BCA Liquid Embolic System is indicated for the embolization of cerebral arteriovenous malformations (AVMs) when presurgical devascularization is desired.

CONTRAINDICATIONS

SEPARATE USE OF THE INDIVIDUAL COMPONENTS OF THE TRUFILL® N-BCA LIQUID EMBOLIC SYSTEM IS CONTRAINDICATED. THESE COMPONENTS MUST BE USED AS A SYSTEM.

TRUFILL® ETHIODIZED OIL ALONE SHOULD NOT BE INJECTED:

- **INTRAVASCULARLY**
- **INTRATHECALLY**
- **INTRABRONCHIALLY.**

The use of the TRUFILL® n-BCA Liquid Embolic System is contraindicated when any of the following conditions exist:

- When optimal catheter placement is not possible.
- When a previous history of reactions to cyanoacrylates exists.
- When a previous history of hypersensitivity to ethiodized oil exists.
- When a previous history of reactions to iodine exists.
- When provocative testing indicates intolerance to the occlusion procedure.
- When vasospasm stops blood flow.

WARNINGS

- The safety and effectiveness of the TRUFILL® n-BCA Liquid Embolic System as a long-term implant has not been established.
- Performing therapeutic embolizations to occlude blood vessels is a high risk procedure. The procedure should be carried out under the direction of personnel with interventional training and thorough knowledge of angiographic techniques.
- Therapeutic embolization should not be performed when high blood flow precludes safe infusion of embolic agent.
- Fluoroscopic determination of the radiopacity of the TRUFILL® n-BCA Liquid Embolic System by comparison with a similar syringe containing contrast prior to

injection is essential. Inadequate visualization of the n-BCA mixture may cause inappropriate embolization.

- TRUFILL® n-BCA is a fast-setting adhesive capable of adhering to most body tissues. It will polymerize in the presence of anionic media, such as any body fluids or tissues. Proper handling is required to avoid premature polymerization and occlusion of the delivery system or adherence of the catheter tip to the vessel wall.

- TRUFILL® Ethiodized Oil should NEVER be used as a radio-opaque contrast agent to assess hemodynamics and should be used ONLY to prepare the TRUFILL® n-BCA Liquid Embolic System.

- AVM embolization may influence blood flow patterns, thereby subjecting arteries supplying the AVM or the brain proximal to the AVM to increased pressures. Increased arterial pressures could result in hemorrhagic complications.

- Laboratory studies have determined that TRUFILL® Ethiodized Oil may elute from the device over time.

- Life threatening and fatal reactions may occur without warning. At all times a fully equipped emergency cart and resuscitation equipment should be readily available, and personnel competent in recognizing and treating reactions of all severity should be on hand.

PRECAUTIONS

- Store in a cool, dark, dry place.

- Do not use if package is open or damaged.

- Use prior to "Use Before Date".

- Angiography is necessary for pre-embolization evaluation, operative control and post-embolization follow-up.

- Verify that the TRUFILL® n-BCA is a clear and free-flowing liquid prior to use. Material that is thickened or discolored should be discarded. It is recommended to use a 21 or 23 gauge needle to aspirate the TRUFILL® n-BCA into an appropriate injection syringe.

- TRUFILL® n-BCA will adhere to most surfaces. Avoid contact with non-disposable surfaces or surfaces that can not be cleaned with acetone.

- Gloves and eye/face protection are recommended when handling TRUFILL® n-BCA.

- Verify that the catheters and accessories used in direct contact with the TRUFILL® n-BCA are clean and compatible with the material and do not trigger polymerization or degrade with contact. Refer to "Accessories" under the "Recommended Procedure" section of these Instructions for Use.

- Do not use with any device containing polycarbonate. Cyanoacrylates cause polymers containing polycarbonate to deteriorate.

TRAINING

Serious, including fatal, consequences could result with the use of the TRUFILL® n-BCA Liquid Embolic System without adequate training. Contact your Cordis Neurovascular, Inc. sales representative for information on training courses.

ADVERSE EVENTS

A total of 104 patients (52 TRUFILL® n-BCA Liquid Embolic System, 52 PVA control) were enrolled for safety evaluation in a clinical trial for the treatment of cerebral AVMs. Two subjects who were randomized to PVA, but who received n-BCA after failed attempts to effectively embolize with PVA, have their complications listed (n-BCA or PVA) as to when they occurred, i.e., during embolization or during surgical resection. Four of the five complications these patients experienced occurred during the PVA embolization stage and therefore are listed as PVA complications. One complication (other-considerable bleeding) occurred during resection after n-BCA embolization and therefore is listed as an n-BCA complication. Therefore, the number of patients used for calculation of the incidence of adverse events in the n-BCA group is 54. Fifty-two percent of the patients in the n-BCA group and 54% of the patients in the PVA group (n-BCA: 51.9%, N = 28, and PVA: 53.9%, N = 28) had at least one complication. There was one unanticipated adverse device event (UADE) reported for a subject in the n-BCA group during the study, described below (Table 1). Two patients died during the treatment period; one due to cerebellar hemorrhage (n-BCA) and the other due to intracerebral hemorrhage (PVA), and 2 patients (PVA) died post-resection. The treatment period was defined as from presurgical embolization up through surgical resection. All reported adverse events which occurred in the TRUFILL® n-BCA Liquid Embolic System cohort in the pivotal clinical study are listed in Table 1. The adverse events are listed in descending order according to frequency as observed for the study treatment group.

Table 1

Incidence of Complications		
Complications	**n-BCA (N=54)**	**PVA (N=52)**
Seizure	5 (9.3%)	5 (9.6%)
Catheter glued inside vessel	4 (7.4%)	0 (0.0%)
Late Polymerization	3 (5.6%)	0 (0.0%)
Occluded Catheter	3 (5.6%)	5 (9.6%)
Parenchymal hemorrhage	3 (5.6%)	6 (11.5%)
Vasospasm	3 (5.6%)	7 (13.5%)
AVM rupture	2 (3.7%)	1 (1.9%)
Early Polymerization	2 (3.7%)	0 (0.0%)
Inability to subselect vessel	2 (3.7%)	4 (7.7%)
CVA (stroke)	2 (3.7%)*	3 (5.8%)
Death	1 (1.9%)	3 (5.8%)
Hematoma	1 (1.9%)	1 (1.9%)
Incorrect vessel(s) occluded	1 (1.9%)*	0 (0.0%)
Infection/Inflammation	1 (1.9%)	0 (0.0%)
Over-the-wire system could not be advanced	1 (1.9%)	1 (1.9%)
Thromboembolism	1 (1.9%)	1 (1.9%)
Vessel dissection	1 (1.9%)	1 (1.9%)
Vessel perforation	1 (1.9%)	3 (5.8%)
Cranial ischemia (TIA)	0 (0.0%)	2 (3.8%)
Catheter rupture	0 (0.0%)	1 (1.9%)
Failure to access vessel	0 (0.0%)	2 (3.8%)
Flow too high for safe infusion of embolic agent	0 (0.0%)	2 (3.8%)
Headache	0 (0.0%)	2 (3.8%)
Pulmonary embolism	0 (0.0%)	1 (1.9%)
Subarachnoid hemorrhage	0 (0.0%)	2 (3.8%)
Subject failed provocative test	0 (0.0%)	1 (1.9%)
Subject uncooperative	0 (0.0%)	2 (3.8%)
Other	9 (17.3%)*	9 (17.3%)

*One n-BCA patient was discontinued due to an unanticipated adverse device effect. A small amount of glue refluxed into the proximal middle cerebral artery and embolized into branches of the middle cerebral artery. The patient developed a neurologic deficit with aphasia and hemiparesis. This event resulted in permanent disability and the patient was determined not to be an appropriate surgical candidate due to neurological status.

Adverse events, which may be associated with embolization procedures (including those observed during the clinical study), may occur at any time during or after the procedure.

These adverse events include (in alphabetical order): allergic reaction, AVM rupture, catheter glued inside vessel, death, early polymerization, headache, hemorrhage, infection/inflammation, late polymerization, neurological deficits, occluded catheter, passage of embolic material into normal vessels adjacent to the lesion, pulmonary embolism, seizure, stroke or cerebral infarction, thromboembolism, vasospasm, vessel dissection, and vessel perforation.

CLINICAL STUDY

Study Design

A prospective, multi-center, single-blind, randomized study was conducted to determine if the TRUFILL® n-BCA Liquid Embolic System was as safe and effective as poly-vinyl alcohol (TRUFILL® PVA) for use in the obliteration of cerebral AVMs when pre-surgical devascularization is desired. The primary effectiveness endpoint was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded) as determined by the angiographic core laboratory. Secondary effectiveness endpoints were the length of time to resect the AVM and the number of transfusions required/total blood loss during the surgery. Primary safety outcomes for comparison to control treatment were the incidences of device-related complications, procedural complications, intracranial events, and unanticipated adverse device effects. Other safety measures, clinical neurological examinations, Glasgow Outcome Scores, and NIH Stroke Scale scores, were summarized at each of the follow-up time periods: post-procedure, pre-surgery, and post-surgery. Patients enrolled in the study were those who had an AVM that required preoperative devascularization as determined angiographically. Patients with Spetzler-Martin grade III, IV and V AVMs were treated, and patients with grade I and II lesions were treated if the anticipated benefit of the embolization was greater than the risk of the embolization procedure, and if the AVM feeding pedicle was located in an area that was difficult to surgically access. Conjunctive therapy using coils was permitted prior to embolization to slow the flow rate (if needed) or if a portion of the AVM contained blood vessels that were larger than the largest size of PVA available. Patients who had been embolized with PVA or cyanoacrylate previously and patients with a known sensitivity to iodine containing contrast reagents were excluded from the study.

Patient Accounting

A total of 104 subjects were enrolled into the study, 52 patients were randomized into each treatment group. Three subjects of the PVA group were determined to be unevaluable for the effectiveness analysis. Two crossover subjects were randomized to PVA, but were treated with n-BCA and one PVA subject was not used for effectiveness analyses due to inadequate source documentation. Four n-BCA subjects were not embolized and therefore not included in the effectiveness analyses. Two subjects were not embolized due to an inability to subselect the feeder vessel. One subject was not embolized because the physician deemed the location and type of AVM was too dangerous to embolized. Finally, one subject was embolized with coils at stage 1 and was to receive n-BCA during stage 2 but withdrew consent. Therefore the total number

of subjects who were included in the primary effectiveness endpoint analysis was 97, 48 subjects in the n-BCA group and 49 subjects in the PVA group. The safety data set included 54 n-BCA and 52 PVA subjects. Two subjects who were randomized to PVA, but who received n-BCA after failed attempts to effectively embolize with PVA, have their complications listed (n-BCA or PVA) as to when they occurred, i.e., during embolization or during surgical resection. Four of the five complications these patients experienced occurred during the PVA embolization stage and therefore are listed as PVA complications. One complication (other-considerable bleeding) occurred during resection after n-BCA embolization and therefore is listed as an n-BCA complication.

Methods

Pre- and post-embolization angiograms were obtained to determine the amount of occlusion achieved. The angiograms were sent to the angiographic core laboratory where anterior/posterior (AP) and lateral views of the nidus and selective arteriograms of the selected feeding pedicles were evaluated to determine the extent of embolization.

Primary Effectiveness Results

The primary effectiveness endpoint was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded). Staged embolizations (more than one embolization procedure per subject) were allowed. The mean percent reduction in lesion volume and number of feeding vessels occluded per subject and per stage are listed in the following table 2. The value of N provided in parentheses represents the number of patients or stages without missing data that were used for the effectiveness analyses.

Table 2

Lesion Volume Reduction and Feeder Vessel Occlusion Per Subject and Per Stage, By Treatment				
	Subject		**Stage**	
	n-BCA	**PVA**	**n-BCA**	**PVA**
Mean Percent Reduction in Lesion Volume	79.4 (N=47)	86.9 (N=47)	81.1 (N=71)	79.9 (N=76)
Mean Number of Feeding Vessels Occluded	2.2 (N=48)	2.1 (N=45)	1.5 (N=72)	1.3 (N=72)

Secondary Effectiveness/Safety Results

Additional parameters assessed included the time of resection and the blood volume replacement needed (units of blood, fluid/colloid, or amount from cell saver). Results for the time of resection and blood volume replacement are reported below.

Table 3

Summary of Data During Surgery-Time to Resect AVM and Volume Blood Replacement Needed

	n-BCA [+] (N=52)	PVA [x] (N=49)	Total (N=101)	
Was AVM resected?				
Yes	49 (92.5%)	48 (92.3%)	97 (92.4%)	
No*	4 (7.5%)	4 (7.7%)	8 (7.6%)	
Time to resect AVM (min)				
N	47	46	93	
Mean	393.9	401.3	397.5	
Median	373.0	357.5	365.0	
Volume Replacement Needed: Units of blood or blood product				
N	47	44	91	
Mean	1.1	3.1	2.0	
Volume Replacement Needed: Fluid/colloid (mL)				
N	47	47	94	
Mean	3683	3597	3640	
Volume Replacement Needed: Amount from cell saver (mL)				
N	41	40	81	
Mean	48.8	181.8	114.4	

[+] One n-BCA subject underwent multiple resections.
[x] Two PVA subjects underwent multiple resections. One subject had an aborted resection after the dura was opened, then underwent true resection at a later date.
* In addition, one crossover subject (PVA to n-BCA) was not resected.
Note: Column headings show number of subjects; however, percentages are based on total number of procedures, a total of 105 (53 n-BCA and 52 PVA).

HOW SUPPLIED

The TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System kit is available in two different kit configurations. One kit consists of two 1-gm tubes of TRUFILL® n-BCA, one 10cc-vial of TRUFILL® Ethiodized Oil and one 1-gm vial of TRUFILL® Tantalum Powder. The second kit includes one 1-gm tube of TRUFILL® n-BCA, one 10cc-vial of TRUFILL® Ethiodized Oil and one 1-gm vial of TRUFILL® Tantalum Powder. In addition, the n-BCA component is available individually in the event that additional product is necessary to complete a cerebral arteriovenous malformation embolization procedure.

STORAGE AND HANDLING

The components of the kit should be stored in a cool, dark, dry place. Remove the components from the carton only upon use. Protect the TRUFILL® Ethiodized Oil from light.

DIRECTIONS FOR USE

Recommended Accessories

- The TRUFILL® n-BCA Liquid Embolic System is designed to be delivered under fluoroscopy to the targeted lesions through the following infusion catheters: Regatta® flow guided infusion catheters, Prowler® family of microcatheters, and Transit® family of microcatheters.

- The TRUFILL® n-BCA with TRUFILL® Ethiodized Oil and, if necessary, TRUFILL® Tantalum Powder mixture should be prepared using a 1 – 10cc syringe(s) made of polyethylene or polypropylene.

Caution: Do not use with syringes containing polycarbonate. The user should contact the syringe manufacturer to verify syringe material.

- To inject the mixture through the infusion catheter, a 1 – 3cc syringe with luer lock made of polyethylene or polypropylene is recommended.

Caution: Do not use with syringes containing polycarbonate. The user should contact the syringe manufacturer to verify syringe material.

- A 21 or 23 gauge needle is recommended to aspirate and/or transfer the TRUFILL® n-BCA, the TRUFILL® Ethiodized Oil and the mixture.

- A sterile 25 to 50cc glass beaker or equivalent is recommended as the mixing container to prepare the mixture.

Pre-Embolization

Serious, including fatal, consequences could result with the use of the TRUFILL® n-BCA Liquid Embolic System without adequate training. Contact your Cordis Neurovascular, Inc. sales representative for information on training courses.

1. Prior to use, perform baseline angiography to determine the vascular supply to the lesion. The angiogram should demonstrate the route of the catheter entry as well as identify relevant collateral circulation.

2. Introduce the infusion catheter according to standard technique. Position the infusion catheter as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.

3. Perform contrast injections to assess hemodynamics prior to embolization.

Caution: The TRUFILL® Ethiodized oil should NOT be used as a radio-opaque contrast agent to assess hemodynamics and should be used only to prepare the TRUFILL® n-BCA Liquid Embolic System. TRUFILL® Ethiodized Oil is CONTRAINDICATED for intravascular, intrathecal or intrabronchial use.

Recommended Mixtures

4. Radiopacification of the TRUFILL® n-BCA is accomplished by adding TRUFILL® Ethiodized Oil and TRUFILL® Tantalum Powder to the TRUFILL® n-BCA. These additives will also extend the polymerization time of the TRUFILL® n-BCA.

5. Recommended ratios of TRUFILL® n-BCA to TRUFILL® Ethiodized Oil and TRUFILL® Tantalum Powder vary depending on the location of injection (feeding pedicle or intranidal), the diameters of the pedicle and nidal component supplied, tortuosity/linearity of the pedicle, presence of AV fistulae, and flow rates. Higher concentrations of TRUFILL® Ethiodized Oil increase the polymerization time, which allows the physician to penetrate the nidus more distally. Higher concentrations of TRUFILL® n-BCA result in a faster polymerization rate, which will allow the physician to embolize the nidus more proximally. Ratios used in the prospective, randomized clinical study of the TRUFILL® n-BCA Liquid Embolic System varied from 10% - 70% n-BCA and 30% - 80% ethiodized oil by volume. The following guidelines are recommended:

Recommended Mixtures (Listed volumes based on a total volume of 1.0 cc – actual total volumes may vary)			
Conditions	**TRUFILL Ethiodized Oil : n-BCA Ratio**	**TRUFILL Ethiodized Oil Volume (cc)**	**TRUFILL n-BCA Volume (cc)**
Intranidal injections without AV fistulae or high flow rates, in order to more deeply penetrate the nidus	3:1(75% Eth. Oil/25% n-BCA)	0.75	0.25
	2:1(67% Eth. Oil/33% n-BCA)	0.67	0.33
Feeding pedicle injections close to the nidus, at high flow rates where venous opacification occurs on contrast injections within ½ second	1:1(50% Eth. Oil/50 n-BCA)	0.50	0.50*
	1:2 (33% Eth. Oil/67% n-BCA)	0.33	0.67*
	* TRUFILL Tantalum Powder may also be added to TRUFILL Ethiodized Oil to augment radiopacity. **TRUFILL Tantalum Powder should not be used alone with TRUFILL n-BCA.** At higher TRUFILL n-BCA concentrations (>50%), addition of up to 0.5g TRUFILL Tantalum Powder is advised.		

Note: If feeding pedicle injections suggest an AV fistula where venous opacification occurs on contrast injection within 1/3 second, placement of a coil(s) to reduce flow should be considered prior to n-BCA injection. Coil placement was used in 15 of 77 (19%) treatment stages during the TRUFILL® n-BCA Clinical Study.

Preparation of Mixture

6. To prepare the TRUFILL® n-BCA, attach the self piercing cap to a luer lock syringe and then attach the other end of the cap (with the syringe connected to it) to the TRUFILL® n-BCA tube. While screwing the cap onto the tube you will first feel resistance which will ease when the seal of the tube is punctured. Continue twisting the cap onto the tube until the next time the resistance builds up again, signaling a proper seal between the syringe, cap, and tube. To avoid spilling the TRUFILL® n-BCA, keep the tube-crimped side down and the cap with the syringe up until a proper seal is achieved. To withdraw the TRUFILL® n-BCA, turn the syringe-cap-tube assembly to the tube-crimped side up and extract the desired amount of TRUFILL® n-BCA into the syringe.

7. Inspect the TRUFILL® n-BCA to verify that it is clear and free flowing. Discard any material that contains particulate matter, is thickened, or discolored prior to use.

8. Place a sterile alcohol wipe around the neck of the TRUFILL® Ethiodized Oil vial and snap the top off.

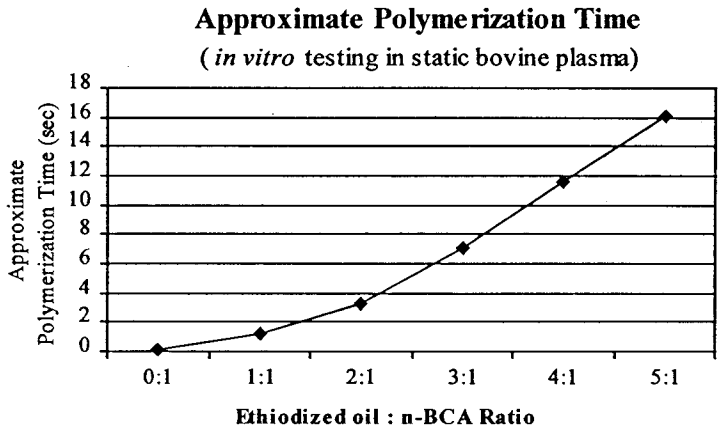
9. Put the desired amount of TRUFILL® Ethiodized Oil and, if necessary, TRUFILL® Tantalum Powder into a clean, sterile glass beaker. Mixing can be achieved by aspirating in and out of a syringe until the mixture appears homogenous.

Caution: The radiopacifying agents must be thoroughly mixed prior to the addition of the TRUFILL® n-BCA. TRUFILL® Tantalum Powder should not be used alone with TRUFILL® n-BCA.

10. Add the desired amount of TRUFILL® n-BCA to the sterile glass beaker. Mix thoroughly as described above until the mixture appears homogenous.

Warning: Polymerization time, viscosity, and injection technique are interrelated and affect the progress of the embolization. The appropriate formulation of any additives is dependent upon the expert evaluation of the relationship of anatomy, hemodynamics, and the catheter system. The following graph illustrates the polymerization rates obtained during *in vitro* testing in static bovine plasma.

Warning: A 0:1 TRUFILL® Ethiodized Oil to TRUFILL® n-BCA ratio should never be used. Refer to the "Recommended Mixtures" section for recommended ratios.



11. To determine whether your mixture is sufficiently radiopaque for visualization compare it fluoroscopically to a similar syringe full of contrast media.

Injection of Mixture

12. Prepare the infusion catheter by thoroughly rinsing the outside of the catheter hub and flushing the catheter with a 5% Dextrose solution in water.

Note: It is not recommended to rinse the glass beaker and/or the syringes with 5% Dextrose prior to use. Prolonged contact of TRUFILL® n-BCA with 5% Dextrose could initiate the polymerization process.

13. Aspirate the mixture into an appropriate injection syringe through a 21 or 23-gauge needle to verify no material is agglomerated. Verify that the mixture is well suspended and free of air bubbles.

14. Positioning the syringe tip slightly upwards (this will minimize the potential for agglomerated tantalum to obstruct the catheter lumen), inject the mixture through the infusion catheter using hand control and high resolution fluoroscopic monitoring.

Warning: If resistance is met during injection, do not attempt to clear or overcome the resistance by applying increased pressure. If this occurs, determine the cause of resistance and remove the catheter, if necessary. Applying increased pressure could result in rupture of the catheter and deposition of the TRUFILL® n-BCA Liquid Embolic System in an undesired area.

15. After injection is completed, immediately aspirate with the injection syringe and rapidly withdraw the catheter to prevent adherence of the catheter tip and to ensure no unpolymerized mixture will leak out during catheter withdrawal.

Note: Should the microcatheter tip become glued to the intracranial site, cut the microcatheter at the hub and remove the guiding catheter. Fix the microcatheter to the groin site. The microcatheter may then be removed during surgical resection of the AVM. If the microcatheter fractures during removal, distal migration or coiling of the microcatheter fragment could occur. Same-day surgical AVM resection should be considered to avoid the risk of thrombosis.

16. Following each injection, discard the infusion catheter.

17. Discard any opened, unused TRUFILL® n-BCA, TRUFILL® Ethiodized Oil, and TRUFILL® Tantalum Powder.

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